

and 41-44 of copending application serial no. 09/183824.

No action is believed required by Applicant as the alleged conflicting claims have not in fact been patented.

4-5 The Rejection of the Claims under 35 U.S.C. 103(a)

The Office has rejected claims 1-9 and 25-29 under 35 U.S.C. 103(a) as being unpatentable over Kumpel et al., (1994) Hum. Antib. Hybridomas 5(3 and 4):143-151 (Kumpel), in view of US patent 5,834,251 by Maras et al. (Maras) and prior art disclosed in the specification.

The Office contends that Kumpel teaches antibody preparations wherein the vast majority of oligosaccharides found on the antibodies in the preparations are G2 oligosaccharides. (Paper 26, page 3). The Office further contends that Kumpel teaches that antibodies with predominantly G2 oligosaccharides have increased lysis of target cells in comparison to the same antibodies produced in a manner that results in low levels of G2 oligosaccharides. (Paper 26, page 3). The Office has directed Applicant's attention to Figure 3 of Kumpel. The Office further contends that Maras et al. teach that a  $\beta$ -1,4 galactosyltransferase enzyme can be used to modify the oligosaccharide profile on a glycoprotein. (Paper 26, page 3). The office cites the specification for disclosure of clinical uses of various antibodies. In sum, the Office claims that it would have been prima facie obvious to one of ordinary skill in the art at the time the present invention was made to have created the claimed invention because Kumpel teaches that antibodies with predominantly G2 oligosaccharides have increased lysis of target cells and Maras teaches methods of producing antibodies to produce antibodies with less G1 and G0 oligosaccharides. Applicants respectfully traverse.

Applicants respectfully submit that Office has failed to establish a prima facie case of obviousness. It is well settled that obviousness cannot be established by combining elements of prior art references absent some teaching, suggestion or

incentive supporting the combination. In arriving at its conclusions, Applicants submit that the Office has impermissibly selected portions of the cited references, in view of Applicant's disclosure, without considering what the references themselves would suggest to the skilled artisan.

The Office contends that the statement by Kumpel that

"hypergalactoylated" anti-D (LD BRAD-3) promoted greater FcRI and FcRIII-mediated lysis of erythrocytes in ADCC assays than the anti-D with a lower galactose content (HD-BRAD-3). (Kumpel page 149)

provides the motivation to produce the claimed invention in view of the disclosure of Maras that  $\beta$ -1,4 galactosyltransferase enzymes may be used to alter glycosylation patterns of recombinantly produced antibodies. However, while Kumpel states that antibodies produced by low cell density (LD) serum free culture contain a high percentage of oligosacchride chains bearing two galactose residues and that these

"hypergalactosylated" antibodies demonstrated greater Fc receptor mediated lysis than antibodies produced by high cell density (HD) serum free culture, Kumpel states that human monoclonal antibodies produced in high density cell (HD) culture have oligosaccharide structures that more closely resemble normal serum IgG. (Kumpel, page 149). Kumpel states:

Structural oligosacchraide analysis of the two serum-free preparations of BRAD-3 (LD and HD) revealed marked differences in glycosylation of the human anti-D Mabs resulting from changes in the growth of the B-lymphoblastoid cells (Table 1). Low density culture produced IgG with a high content of digalactylated (G2) strucures (77%), while the glycosylation profile of the anti-D secreted at high cell densities resembled more closely that of normal human serum IgG (with about 30% G2). (Kumpel page 149, paragraph bridging the columns, emphasis supplied).

Kumpel provides in conclusion:

The two human anti-D MABs produced in this way [hollow fiber culture], BRAD-3 and BRAD-5, were found to have oligosaccharide structures that were similar

to normal serum IgG, and to have good Fc receptor-mediated functional activity both in vitro and in vivo. (Kumpel page 150, last sentence).

In view of the foregoing, Applicants submit that Kumpel would not suggest to the skilled artisan that a preparation other than one that closely resembles normal human serum be prepared. In fact, Kumpel states that "hyperglycosylated" preparations, in general, "result in extremely rapid clearance of a glycoprotein from serum" (Kumpel, page 150, second full paragraph). Whether or not Maras supplies teaching of methods for modifying glycosylation patterns of recombinantly produced antibodies, Applicants submit that the Office has impermissibly used Applicants disclosure to supply motivation to produce antibody preparations such as the claimed preparations.

Moreover, assuming arguendo, that Kumpel suggests that a particular preparation be prepared, Kumpel does not suggest that the skilled artisan prepare a preparation wherein the amount of glycoprotein containing a G1 and G0 oligosaccharide in the preparation does not exceed 10% by weight of the preparation. Further, Kumpel does not suggest that the skilled artisan employ techniques beyond the cell culture techniques specifically disclosed nor that the skilled artisan turn to a technique such as the one that may be disclosed by Maras to alter glycosylation profiles of antibodies produced in cell culture.

Therefore Kumpel alone or in combination with Maras and the specification fail to provide the motivation to produce Applicant's claimed compositions but rather suggest only that some heterogenous glycoprotein preparation can be prepared.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the pending rejection of the claims under 35 U.S.C. 103.

#### CONCLUSION

Applicants respectfully request that the foregoing remarks be considered and entered in the file history of the above-

identified application. It is submitted that the claims are in condition for allowance. It is therefore earnestly solicited that such a final favorable disposition is made. The Examiner is invited to telephone Jeffrey S. Kubinec, (Reg. No. 36,575) at (650) 225-8228 if deemed helpful to clarify and advance prosecution.

Respectfully submitted,  
GENENTECH, INC.

Date: May 7, 2003

By: 

Jeffrey S. Kubinec

Reg. No. 36,575

Telephone No. (650) 225-8228



09157

PATENT TRADEMARK OFFICE